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Hyperalimentation in Cancer

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A growing body of work has been addressed to the hypothesis that because patients with cancer who have poor nutritional status have a worse prognosis, increased nutritional support in these patients will result in better tolerance of surgical interventions, chemotherapy and radiation therapy, and a better outcome from the cancer. Although the hypothesis is an attractive one, there is only a single well-conducted, randomized, prospective trial to date that shows that active nutritional support is of benefit in the therapy of patients with cancer. Based on this review of the literature, it is felt that though cachexia is clearly of negative import in patients with cancer, there is little evidence to support the hypotheses that any nutritional support changes the outcome or the course of therapy of patients with cancer. It seems reasonable to continue the nutritional support to cachectic patients with cancer concomitant with specific anticancer therapy, but supportive nutritional therapy alone with postponement of specific anticancer treatment, as in awaiting weight gain or anabolism, cannot be justified with the current state of the art.

MOST PATIENTS with cancer lose weight during the course of their disease and most will also have anorexia. It has long been felt, but only recently clearly established, that this weight loss is an important prognostic determinant of morbidity and mortality.[1-6] Determined efforts have been made during the past decade to treat this cachexia so as to transfer patients from one clinical subset of cancer-bearers to another with a better prognosis based on measurements of nutritional status.[7] Many authors claim that good nutrition is of benefit to cancer patients.[7-9] It has also been reported that nutritional support could make patients with cancer less susceptible to the adverse effects of various antineoplastic therapies.[10-13] Although it is not yet known why patients having cancer die when vital organs such as heart, lungs and liver are uninvolved by neoplasm, death in cancer is most commonly related to infections,[14] where the mortality can reach 65 percent.[15] In this sense improvement in a patient's immunologic defense mechanisms has been considered one of the most beneficial achievements of nutritional support.[11]

The purpose of this review is to evaluate whether the hypothesis that effective nutritional support improves the outcome of cancer treatment is in fact supported by published clinical and experimental data. This review will also deal with the question of whether hyperalimentation is most beneficial to tumor or host.

Cancer Cachexia

Cancer cachexia is not an inevitable manifestation of a tumor's systemic effect on a patient.[14]

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ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
FFA = free fatty acid

It is a descriptive concept, which includes the net effect of several metabolic and hormonal alterations, and may not be specific for a patient with neoplastic disease. It may be that cancer cachexia is indistinguishable from other clinical conditions with cachexia and that the expression "cancer cachexia" is inappropriate.[16] The features of this syndrome have been compared with physiologic reactions accompanying other clinical conditions with cachexia, such as anorexia nervosa, malnutrition, starvation, trauma and infections. However, it has also been assumed that the increased demand of growing mass in a patient (host) may induce certain hormonal and other responses accompanying those of the normal adaptation to stress.[17] As a result, various substrates and compounds are selectively taken up by the tumor, which may act as a glucose[14] or a nitrogen trap[18]; in this manner the tumor induces a depleted nutritional state in the host. Morrison[19] has pointed out that such explanations are nothing more than a complicated way of saying that something additional is growing inside the patient-host. Perhaps the most remarkable aspect of this tumor-host relationship is the inability of the host to respond to this increased energy demand with increased nutritional intake.

The significance of certain factors such as "lipolytic factors"[20,21] and "toxohormones" (which may be released by the tumor tissue)[22-24] as a cause of cancer cachexia has been evaluated in several studies. More recently others have found alterations in the normal central nervous system physiology controlling feeding that may explain anorexia of cancer.[25]

A reasonable conclusion from various hypotheses in the literature is that cancer cachexia is the net result of many different physiologic changes in the metabolic and immunologic response to the stress of unregulated tumor growth and to an often-accompanying anorexia.

The Tumor-Host Effect

Tumor tissue is derived from transformed cells from the host. There is no evidence that tumor tissue possesses unique properties compared with the untransformed host cells in terms of overall cellular metabolism. But the malignant tumor cells lack metabolic capabilities of normal cells, while retaining some properties characteristic of undeveloped fetal tissue. The enzymatic equipment in these transformed cells is most peculiar and leads to differences in cellular metabolism. One of these differences is the diminished ability of tumor cells to oxidize glucose for energy generation and the proportionally increased reliance on glycolysis.[26,27] Although both reactions produce high-energy phosphates (mainly adenosine triphosphate [ATP]), the efficiency is strikingly different. Each molecule of glucose converted to carbon dioxide in normal cellular respiration yields 38 molecules of ATP, whereas the nonoxidative glycolysis produces only two molecules of ATP. Thus the anaerobic fermentation in tumor tissue is 19 times less efficient than the oxidative glucose conversion in normal tissue. From another standpoint the high glycolytic activity in tumor tissue increases the lactic acid load on host tissue, which must be converted to glucose in the liver through a process called gluconeogenesis. Gluconeogenesis is an energy-requiring reaction that consumes six molecules of ATP for each molecule of glucose produced. Expressed in another way, a sixth of the lactate produced by the tumor has to be oxidized to yield the energy for gluconeogenesis. For the tumor-plus-host system this means that for each molecule of glucose converted to lactic acid in tumor tissue, the tumor itself gains two molecules of energy-rich ATP but consumes four molecules of host ATP, which has to be produced elsewhere. This increased turnover of energy substrates is one of the metabolic consequences of the inefficient glucose metabolism in tumor tissue. In short, an inefficient metabolism in terms of coupling of energy occurs. The clinical relevance of these biochemical alterations relates to studies on tumor-bearing animals and cancer patients that have shown increased glucose turnover and gluconeogenesis, and increased cycling of glucose carbons.[28-30] These changes in cellular metabolism may be one explanation for the increased energy expenditure in patients with cancer.[31]

The oncofetal enzyme equipment in tumor tissue makes it an efficient substrate consumer compared with nonmalignant tissue. However, the metabolic rate as such does not seem to be distinctly different from that of other rapidly renewing tissues such as mucosal cells of the gastrointestinal tract. As Costa[32] has pointed out tumor tissue rarely exceeds 2 percent to 3 percent of the body weight of a patient with cancer. With an

overall turnover rate comparable with that of normal rapidly regenerating cells, the tumor cannot be the main cause of cachexia in terms of a "nitrogen trap." It also seems likely that the "energy trap" is related more to tumor-host interaction, with inefficient energy cycling, than to an unusually high metabolic rate with increased energy demands by the tumor cells.

Part of the negative energy state in patients with cancer is associated with increased metabolic processes such as interorgan cycling of glucose carbons, gluconeogenesis, glucose turnover rate and basal metabolic rate.[29,31-35] Increased gluconeogenesis, however, is not specific for cancer disease. From a teleological viewpoint, the body's first priority in the face of the metabolic stress and trauma of an inadequate nutritional supply is to ensure an uninterrupted supply of glucose for the central nervous system and the erythrocytes. Initially, this is carried out by mobilizing glycogen stores and by gluconeogenesis from protein. Glycerol from lipolysis stimulated by norepinephrine is one of the major precursors for gluconeogenesis in cancer.[21] The increased free fatty acid (FFA) concentration decreases insulin-dependent glucose uptake. The insulin effect is also blocked by an increase in growth hormone activity. In clinical situations this pattern of metabolic reaction is seen as insulin resistance[36] as evidenced by high levels of plasma glucose after infusion of glucose solution. The gluconeogenesis from these precursors in cancer results in depleted glycogen stores and greatly reduced lipid stores.[37] Consequently, cancer patients are more vulnerable to acute stress factors such as infections and surgical trauma.

Hyperalimentation

In starved or traumatized patients, immediate nutritional support has become a routine part of treatment. This support often can be adjusted to a patient's metabolic needs in terms of severity of injury—for example, multiplicity of trauma or area of burn size. The duration of need for nutritional support often can be anticipated in an injured patient. In comparison, the point when a change to anabolism with nutritional support can occur in a patient with cancer is very uncertain. By the time a patient is seen, the degree of nutritional deficit is often already much greater. Nutritive therapy or hyperalimentation in cancer patients therefore has been established according to certain standard procedures. This nutritional support is started before specific antitumor therapy with the hope of achieving anabolism in the tumor-host as shown by weight gain and a positive nitrogen balance, which has always been considered favorable. Nonetheless, weight gain can occur without protein gain, and body weight is not a reliable guide to changes in lean body mass.[38] Many factors influence nitrogen balance; for example, bedridden patients may in fact be in a negative nitrogen state without inadequate nutritional support simply because of decrease in activity.

It has long been anticipated that energy-producing nutrients should be given in conjunction with nitrogenous compounds.[39,40] It has also been shown that glucose and amino acids spare more body protein than amino acids alone in patients with cancer who undergo surgical procedures.[41] These findings have been the basis for standard infusion regimens of solutions containing dextrose of 750 to 1,000 grams per day and amino acids at various concentrations. To these infusion solutions vitamins and electrolytes have been added according to established needs. Three fatty acids are considered essential: linolenic, linoleic and arachidonic. Deficiency of these fatty acids leads to skin and wound healing problems and difficulties in metabolizing other fatty acids, resulting in fatty infiltration of the liver.[42,43] Administration of 500 ml of Intralipid (Cutter Medical Division of Cutter Laboratories, Berkeley, CA 94710), 20 percent solution weekly, has been considered sufficient to prevent essential fatty acid deficiency.[43-46] In summary, hyperalimentation in these patients should consist of 500 to 1,000 grams of glucose daily, with the addition of amino acids such as 500 ml of a crystalline amino acid 8.5 percent solution along with electrolytes, vitamins and biweekly fat.

Typically patients receiving hyperalimentation for as few as seven days gain weight. However, it has recently been shown that this weight gain consists mainly of water and fat.[39,47,48] Patients have even been found to lose weight during intravenous administration of nutrients but to increase body-water content. Tumor-hosts have also been known to have disturbed water and electrolyte balance even during ad libitum intake.[49] It can be concluded that weight gain can occur without protein gain in patients who are being fed intravenously and that body weight is not a reliable guide to changes in lean body mass or fat.[50]

High infusion rates of glucose increase the

metabolic rate and carbon dioxide (CO_2) production, which results in self-defeating hypermetabolism.[51-53] It may be that infusion rates of glucose in excess of 5 mg per kg of body weight per minute increase metabolism and lipogenesis. It has also been suggested that a maximum of 60 percent of infused glucose is directly oxidized for energy and that this proportion falls with increasing infusion rates; any additional glucose is converted to fat. Large infusions of glucose may increase the ventilatory load by increasing CO_2 production and water retention. This critical load of 5 mg a minute is exceeded with 500 grams of glucose to a 59-kg (130-pound) patient during 24 hours. However, the studies referred to above are flawed, fail to account for internal cycling and are not universally accepted.

Lipids have been used routinely as calorie sources for many years in certain countries. The rationale for this use involves the ability to deliver a high ratio of calories per volume of infusion solution through peripheral veins, the avoidance of increased fatty liver development caused by high glucose loads and the provision of essential fatty acids. It has recently been shown that the glucose-fatty acid cycle is of questionable physiologic significance in terms of regulating basal glucose and FFA concentrations. Infusing lipids simultaneously with glucose does not decrease the efficiency with which the infused glucose is metabolized.[53] Also, at high infusion rates of glucose, as much as 30 percent of the energy supply is wasted on lipogenesis.[52] The differential effect of various substrates on tumor growth has long been established. However, only recently was a clear-cut beneficial effect of high lipid infusion ratio shown on host tissue maintenance versus tumor growth in tumor-bearing rats.[54] If this effect can be confirmed in cancer patients, it certainly would influence the current policy of providing lipids as a calorie source in oncologic hyperalimentation.

Therapeutic Effects of Nutritional Support

It is interesting to note that high-glucose load regimens have been used in the treatment of hundreds of patients over the years without overt complications. This treatment also has induced striking changes in immunocompetence[9,11] in patients and in experimental tumor-host systems,[55] which has been a criterion for its beneficial effects. The overall favorable outcome, however, of specific antitumor therapy in hyperalimented patients in a controlled, prospective randomized study has been shown in only one study.

In one randomized, controlled, clinical trial of preoperative intravenous nutritional support of patients with stomach or esophageal cancer, a significant effect was found on rates of wound sepsis only. The main conclusion from this study was that although such clinical trials are extremely hard to complete, there seems to be a subset of patients with cancer who benefit more than others from nutritional support.[56] One measurement used to identify this subgroup was the serum albumin concentration.[57] Although isolated laboratory values have have been shown to be useful, the evaluation of the overall effect of nutritional support of hyperalimentation preferably should involve a significant change in the outcome by all types of treatment for the specific tumor in a prospective randomized trial. The number of studies are limited,[10,48,56,58-66a] but a few well-organized retrospective clinical studies do exist, in addition to data gathered from studies on tumor-bearing animals. It is fair to say that there is only one properly conducted randomized prospective trial that shows a statistically significant beneficial effect in tumor patients treated with nutritional support.

A randomized prospective trial has shown that patients undergoing major upper gastrointestinal tract surgical procedures have a lower mortality when preoperative and postoperative hyperalimentation is given as compared with standard therapy. There was no beneficial effect on major complications possibly related to malnutrition, such as wound and anastomotic disruption and sepsis.[66b] Interestingly, this beneficial effect was seen in all patients and not merely in malnourished patients. This study, then, does not totally support the concept that *malnourished* patients are improved by perioperative parenteral nutrition, but argues that all patients with major operations for cancer should be supported by parenteral nutrition.

Several authors have proposed that the conversion of lactate to glucose via the Cori cycle could result in an important energy drain and, as pointed out earlier, could result in futile cycling of glucose and thus contribute to the cachexia of cancer.[14,30,33,67] As the host-organ tissue cells harbor the ability to adapt to low-glucose states that the tumor does not possess, blocking this gluconeogenesis would seem rational antitumor therapy. There are several compounds reported capable of reducing or blocking gluconeogenesis.[68-71] Some

of these inhibitors have been reported to be capable of inhibiting in vivo growth of experimental tumors.[35] It is interesting to note that the host animals in this study by Gold at the same time decreased their total body weight. Unfortunately, completed clinical trials of one of the blocking agents, hydrazine sulfate, have failed to show either direct antitumor effect or nutritional benefits for patients with cancer.[34] A physiologic block of gluconeogenesis might be realized from adequate nutritional support that would suppress gluconeogenesis from amino acids. However, this effect is accompanied by increased glucose cycling,[72] which minimizes any beneficial effect.

In starvation or semistarvation, which in some respects resembles anorexia of cancer, gluconeogenesis is not increased to the same extent as in acute metabolic situations. The central nervous system switches from glucose to the use of ketone bodies as the main energy source. Lipolysis increases with increased free fatty acid content and transport to the liver for oxidation to ketone bodies. However, starvation is a *hypometabolic* state with a reduction in turnover of nutrients and with ketone bodies playing a regulatory role,[73,74] and cancer is a *hypermetabolic* state with increased metabolic turnover. Moreover, ketosis is an uncommon phenomenon in cancer patients and in tumor-bearing animals. In starvation there seem to be reduced cell growth rates. This could possibly be a reaction induced by ketosis.[75] Ketone bodies have also been shown to reduce the growth of malignant cells in growth culture. It therefore has been speculated that induced ketosis in cancer patients by infusion of lipid solutions might be of therapeutic benefit. No controlled data have shown that this is the case, though lipids as energy substrate have been shown to have host-tissue maintenance properties.[54]

Tumor tissue is dependent solely on glucose for its energy production, which is necessary for cell growth and replication. When the availability of glucose is limited, tumor tissue competes successfully with host tissue for glucose substrates via gluconeogenesis not only from tumor-produced lactic acid but also from other sources such as amino acids derived from skeletal muscle. Because of this competition, it would seem difficult on theoretic grounds to starve the tumor by feeding the tumor-bearing host energy-rich nutrients other than glucose (such as fat). There are experimental data indicating that specific substrate compositions may promote host maintenance equivalent to carbohydrate-based nutritional support with significantly less stimulation of tumor growth.[54]

The incomplete metabolic features in tumor tissue also seem to make it susceptible to other forms of substrate differentiation. In vitro studies have shown that methionine deprivation inhibits tumor cell growth from some specific lines without affecting normal cells.[76] This has not yet been confirmed in vivo.

In summary, these is only one beneficial result from prospective randomized studies that have been published. Some of the studies have shown improvement of isolated physiologic measurements such as a decreased rate of wound infections[56] and less of a drop in granulocyte count[62] and leukocyte count[10] in combination with chemotherapy. Only one study has been able to show significantly increased survival.[66b]

Nutrition and Chemotherapy

There has always been a suspicion that tumor tissue would gain more from nutritional support than patient-host tissue. The rationale for this theory is that a growing tissue has a high affinity for substrates and that tumor growth in some instances may be retarded by anorexia of the host and concomitant nutritional shortage. In tumor-bearing animal systems this has been shown to be true, at least during a short period.[77,78] It was also shown that parenteral hyperalimentation induced higher mitotic activity in tumor tissue cells, which indicated that intravenous feeding caused the tumor to undergo faster cellular turnover.[77]

Chemotherapy acts at the cellular level to destroy tumor cells or to prevent their replication. Different antineoplastic drugs act during different phases of the cell cycle. G_1 is the first growth period in which enzymes, structural proteins and organelles are synthesized. During S phase DNA synthesis occurs. G_2 is the second growth phase and in M phase mitosis and cell division occur. Vinblastine and vincristine sulfate are examples of drugs that interfere with mitosis and thus block cell division, whereas 5-fluorouracil interferes with thymidine synthetase resulting in a blockage of DNA synthesis. Cell-cycle-specific drugs act best during proliferation phases and much effort has gone toward planning chemotherapy schedules according to these principles of timing. It has been suggested that nutritional support could stimulate replication of cancer cells, making cell-cycle-specific drugs more effective in treatment. As an

example, methotrexate, a chemotherapeutic agent that inhibits DNA synthesis, was shown to be more effective in a group of rats in which tumor growth rate was increased by nutritional manipulation.[79]

As in all instances in which conclusions are drawn from experimental tumor systems, the ratio of tumor mass to host and the time for tumor development, which may differ in relation to cancer in humans, must be taken into account. For example, if 10 to 20 days of nutritional manipulation seem to change the growth rate of sarcoma in rats, this may be comparable with months of nutritional repletion in patients with cancer. In this context the few proved effects of short-term nutritional support in cancer patients during specific anticancer treatment involve the maintenance of rapidly renewable and vulnerable tissues such as leukocytes and cells of the gastrointestinal mucosa.

Starvation is known to reduce rat liver DNA synthesis.[80] Such a decrease should theoretically decrease a host's susceptibility to the adverse effects of, for example, 5-fluorouracil. When the tumor grows autonomously with priority over the host in situations with limited nutritional supply, its growth is less affected by starvation.[81] Such a theory could argue against the beneficial effects of nutritional support during chemotherapy.[82]

Conclusion

It is necessary to remember that cancer cachexia is the result not only of semistarvation but of a complex metabolic reaction. In tumor-bearing hosts and patients with cancer there are abnormalities in metabolism of energy, carbohydrates, lipids and protein. There are numerous alterations in the activity of host tissue enzymes and changes in endocrine homeostasis and immune mechanisms.[83] Only the complete definitive treatment of the underlying malignant lesion can reverse the cachectic syndrome. From available data it is clear that there are a variety of tumors that affect their hosts differently. So far no conclusive data exist about the type or types of substances or other mechanisms by which the tumor may induce the cachexia syndrome.

The causes of malnutrition in cancer patients can be summarized as follows: anorexia, increased basal metabolic rate or hypermetabolism in the host, the nutritional demands of the tumor and effects of oncologic therapy.[84] All these factors lead to cachexia, which has been a challenge for nutritional therapy. Such treatment has been reported of value in certain subgroups of patients with cancer in terms of improvement in the immune status and rate of wound healing.[1,2,9,11,56] However, these patients also appear to respond better to specific antitumor therapy; the nutritional reaction to hyperalimentation thus could be regarded as a prognostic factor. In this regard the hyperalimentation as such is of minor importance as an antitumor treatment regimen.[12,60,85]

The finding that hyperalimentation mainly leads to accumulation of adipose tissue has been regarded as an indication of a block in repletion of lean body mass in cancer patients.[86] However, the same reaction is also seen in patients without cancer, indicating that this may be a general reaction to short-term energy loads in states of disturbed metabolism of any cause.[38,47]

The evidence that nutritional support of patients with cancer is of any benefit in increasing survival or causing significant changes in metabolic values associated with higher response rates to various forms of specific antineoplastic therapy is marginal at best.[48,61,63,85-87] There is also no clear-cut evidence of significantly accelerated tumor growth rate under the influence of clinical hyperalimentation.[55,72,88-90] As several reports have been able to show, nutritional therapy may not significantly prolong life but it can improve the quality of life,[31] in part by improving a patient's ability to tolerate the side effects of various forms of treatment.[1,9-13,56] It seems reasonable, therefore, to continue the nutritional support to cachectic cancer patients concomitant with specific anticancer therapy. Supportive nutritional therapy alone, however, or postponing specific anticancer treatment (awaiting weight gain or anabolism) cannot, with today's knowledge, be justified.

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